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α2-Adrenoceptor Antagonists Reverse the 5-HT_2 Receptor Antagonist Suppression of Head-Twitch Behavior in Mice

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MATSUMOTO, K., M. MIZOWAKI, S. THONGPRADITCHOTE, Y. MURAKAMI AND H. WATANABE. *α2-Adrenoceptor antagonists reverse the 5-HT_2 receptor antagonist suppression of head-twitch behavior in mice.* PHARMACOL BIOCHEM BEHAV **56**(3) 417–422, 1997.—The α2-adrenoceptor agonist clonidine, as well as 5-HT_2 receptor antagonists, reportedly suppress 5-HT_2 receptor-mediated head-twitch behavior. We investigated the effect of α2-adrenoceptor antagonists on the suppressive action of 5-HT_2 receptor antagonists in mice pretreated with the noradrenaline toxin 6-hydroxydopamine (6-OHDA) or the 5-HT synthesis inhibitor *p*-chlorophenylalanine (*p*-CPA). In normal mice, idazoxan (0.08-0.2 mg/kg, IP) or yohimbine (0.2-2.0 mg/kg, IP), both α2-adrenoceptor antagonists, had no effect on the head-twitch response caused by 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT; 16 mg/kg, IP), but idazoxan significantly enhanced the response at 0.5 mg/kg. On the other hand, these α2-adrenoceptor antagonists, at doses that had no effect on the basal number of head-twitches (idazoxan 0.2 mg/kg and yohimbine 0.5 mg/kg), significantly attenuated not only the suppressive effect of clonidine (0.01 mg/kg, IP) on head-twitch response but also that of the 5-HT_2 receptor antagonist ritanserin (0.03 mg/kg, IP). Moreover, idazoxan (0.2 mg/kg) also significantly reversed the inhibition by 0.01 mg/kg (IP) ketanserin, a selective 5-HT_2 receptor antagonist. Pretreatment with 6-OHDA plus nomifensine but not with *p*-CPA significantly attenuated the effect of idazoxan (0.2-0.5 mg/kg) on the ritanserin inhibition of the head-twitch response. Prazosin, an α1-adrenoceptor antagonist, dose-dependently suppressed the response, and the effect of prazosin (1.25 mg/kg) was significantly attenuated by 0.5 mg/kg idazoxan. These results indicate that endogenous noradrenaline is involved in the apparent antagonistic interaction between selective α2-adrenoceptor antagonists and 5-HT_2 receptor antagonists in the head-twitch response, and suggest that noradrenaline stimulation of α1-adrenoceptors may be involved in this apparent antagonism.

Head-twitch behavior Mice Noradrenaline α2-Adrenoceptor 5-HT_2 receptor

5-HT_2 receptors in the central nervous system are involved in psychiatric disorders such as depression, anxiety, schizophrenia, sleep disorders, and hallucination in humans [1,7,8,24]. In rodents, 5-HT_2 receptor agonists and 5-HT precursors are known to produce "head-twitch response" [3], and this behavior provides an experimental model to study 5-HT_2 receptor function in the brain [11,22,23].

Central noradrenergic systems have been implicated in the head-twitch behavior. The α2-adrenoceptor agonists such as clonidine inhibit the behavior in mice, while the α2-adrenoceptor antagonists produce the opposite effect [13,16]. Moreover, although there are controversial reports [10], blockade of α1-adrenoceptor and stimulation of β-adrenoceptor have been reported to suppress and enhance the behavior, respectively [13–15], suggesting a facilitatory role of these receptor subtypes in the head-twitch behavior. However, it is not yet clear to what extent endogenous noradrenaline contributes to the regulation of head-twitch behavior, since the effects of noradrenaline depletion on the 5-HT_2 receptor-mediated head-twitch behavior are controversial [21]. Moreover, recent evidence implicates endogenous 5-HT in the appearance of head-twitch response caused by 5-HT_2 receptor agonists. For example, the inhibition of the head-twitch response by 8-hydroxy-2-(di-n-propylamino)tetraline (8-OH-DPAT), a selective 5-HT_{1A} receptor agonist, is reportedly attenuated by 5-HT depletion [5]. In addition, the 5-HT receptor agonist quipazine-induced head-twitch response can be potentiated by inhibition of monoamine oxidase activity [18].

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In this study, we examined the effects of selective α2-adrenoceptor antagonists on the inhibition of 5-HT_2 receptor-mediated head-twitch response by selective 5-HT_2 receptor antagonists in 6-hydroxydopamine (6-OHDA)- or *p*-CPA-pretreated mice to further elucidate the role of endogenous noradrenaline and 5-HT in the regulation of the response.

METHODS

Animals

Male ddY mice (Japan SLC, Shizuoka, Japan) were obtained at the age of 4 wk. They were housed in groups of 15 per cage (35 × 30 × 16 cm), on a 12-h light/dark cycle (lights on: 0730-1930) at 24 ± 1°C for at least 1 week before starting the experiments. Food and water were given ad lib.

Drugs

Drugs were obtained from the following sources: clonidine HCl, idazoxan HCl, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), prazosin HCl and 6-hydroxydopamine HBr (6-OHDA) (Sigma Chemical Co., St. Louis, MO), ritanserin, ketanserin tartrate and nomifensine maleate (Research Biochemicals Inc., Natick, MA), yohimbine HCl (Nacalai Tesque Inc., Kyoto, Japan). 5-MeO-DMT was dissolved in saline by adding a few drops of 1N HCl, and the pH was adjusted up to 4.7 with 1N NaOH. Ritanserin and ketanserin were dissolved in a small amount of ethanol and then diluted with saline. Prazosin was suspended in saline containing 0.5% carboxy methylcellulose sodium. 6-OHDA solution was freshly prepared by dissolving in ice-cold saline containing 0.2% ascorbic acid. Other test drugs were dissolved in saline. Drug solutions were prepared just before starting the experiments.

Depletion of Noradrenaline and 5-HT in the Brain

For endogenous noradrenaline depletion, mice were pretreated with nomifensine (5 mg/kg, IP), a selective dopamine uptake blocker, to protect dopaminergic systems. Thirty minutes later, mice were injected intracerebroventricularly (i.c.v.) with 6-OHDA (50 μg/mouse) or the corresponding vehicle. I.c.v. injection was accomplished by inserting a specifically designed injection needle into the lateral ventricle of the mouse brain (about 2 mm lateral and 2 mm caudal to the bregma) according to Haley and McCormick [12]. The injection volume was adjusted to 5 μl/mouse. Seven days after injection, mice were used for the behavioral experiments. Endogenous 5-HT depletion in the brain was achieved according to the method described by Dursun and Handley et al. [5]. Briefly, mice were injected intraperitoneally with 3 doses of *p*-CPA (300 mg/kg, each) 24, 48, and 72 hr before the experiments. Monoamine levels in the brain were determined as previously described [20].

Measurement of 5-MeO-DMT-Induced Head-Twitch Response

Mice were pretreated with test drugs or vehicle 30 min before the experiments, and then individually placed in the observation cages (24x17x12 cm) with a thin sawdust floor covering. Immediately after the injection of 5-MeO-DMT (16 mg/kg, IP), number of head-twitch responses was counted over a 10-min period. The 5-HT_2 receptor antagonists, ritanserin and ketanserin, and the α2-adrenergic drugs, clonidine, idazoxan and yohimbine, were administered s.c. and IP 30 min before 5-MeO-DMT, respectively. The α1-adrenoceptor antagonist prazosin was injected IP 45 min before 5-MeO-DMT.

Statistics

The effects of drugs on the head-twitch responses were analyzed by the Kruskal-Wallis analysis of variance followed by the Mann-Whitney U-test for multiple comparison. Neurochemical data were analyzed by a two-tailed Student's t-test. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Effects of the α2-Adrenoceptor Antagonists on Clonidine-, Ritanserin- and Ketanserin-Induced Inhibition of Head-Twitch Response

Consistent with previous data [2,16], pretreatment with prototypical and selective 5-HT_2 receptor antagonists ritanserin (0.025-0.1 mg/kg, s.c.) and ketanserin (0.005-0.1 mg/kg, s.c.) or with the selective α2-adrenoceptor agonist clonidine (0.01-0.1 mg/kg, IP) dose-dependently suppressed 5-MeO-DMT-induced head-twitch responses (data not shown). Idazoxan (0.08-0.2 mg/kg, IP) or yohimbine (0.2-2.0 mg/kg, IP), both α2-adrenoceptor antagonists, had no significant effect on the head-twitch response (Fig. 1A, B), but idazoxan produced a significant increase in the response at 0.5 mg/kg. These α2-adrenoceptor antagonists, at doses (Idazoxan 0.2 mg/kg and yohimbine 0.5 mg/kg) that had no effect on the 5-MeO-DMT-induced head-twitch response, significantly attenuated the clonidine (0.01 mg/kg) inhibition of head-twitch response (Fig. 1C, D). Moreover, as shown in Fig. 2, both α2-adrenoceptor antagonists significantly reversed the inhibition of the head-twitch response by ritanserin (0.03 mg/kg, s.c.). Idazoxan (0.2 mg/kg, IP) also significantly blocked the inhibitory effect of ketanserin (0.01 mg/kg, s.c.) on the head-twitch response (Fig. 2C).

Effect of Depletion of Noradrenaline and 5-HT on the Apparent Antagonistic Effect of Idazoxan on the Head-Twitch Behavior Suppressed by Ritanserin

The roles of endogenous noradrenaline and 5-HT in the apparent antagonistic interaction between α2-adrenoceptor antagonists and 5-HT_{2A} receptor antagonists in head-twitch response were examined by pretreatment of animals with 6-OHDA plus nomifensine and *p*-CPA, respectively. As summarized in Table 1, pretreatment with 6-OHDA plus nomifensine significantly decreased the contents of noradrenaline in the cortex and brainstem by 91.4 and 27.9%, respectively, without affecting the contents of 5-HT. On the other hand, pretreatment with *p*-CPA significantly decreased the contents of 5-HT in these regions (by 61.5 and 69.4%, in the cortex and brainstem, respectively) without changing the levels of noradrenaline. Depletion of noradrenaline by 6-OHDA plus nomifensine did not significantly alter the basal number of 5-MeO-DMT-induced head-twitches, but it abolished the reversing effect of 0.2-0.5 mg/kg idazoxan on the ritanserin inhibition of the head-twitch response (Fig. 3). In contrast, depletion of 5-HT by *p*-CPA treatment did not alter the basal number of head-twitches caused by 5-MeO-DMT, or attenuated the reversing effect of idazoxan (Fig. 4).

Effect of Idazoxan on the Inhibition of Head-Twitch Response by the α1-Adrenoceptor Antagonist Prazosin

As shown in Fig. 5, the selective α1-adrenoceptor antagonist prazosin (1.25 mg/kg, IP) significantly and dose-dependently

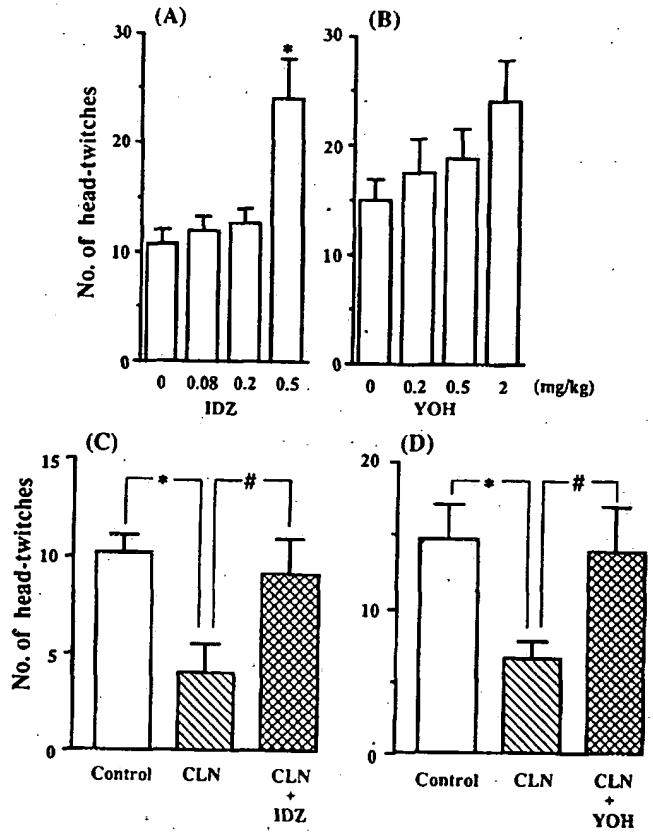

FIG. 1. Effects of selective α2-adrenoceptor antagonists idazoxan and yohimbine on head-twitch response caused by 5-MeO-DMT and on clonidine-induced inhibition of the response in mice. (A, B) Immediately after 5-MeO-DMT (16 mg/kg, IP) injection, the number of head-twitch responses was counted over a 10-min period. Idazoxan (IDZ, 0.05-0.5 mg/kg) or yohimbine (YOH, 0.2-2 mg/kg) was injected IP 30 min before 5-MeO-DMT. (C, D) Clonidine (CLO, 0.01 mg/kg), IDZ (0.2 mg/kg), YOH (0.5 mg/kg) or vehicle was injected IP 30 min before 5-MeO-DMT (16 mg/kg, IP). Each datum represents the mean ± SEM (n = 10). *$p < 0.01$ vs. vehicle control. #$p < 0.05$ vs. clonidine alone.

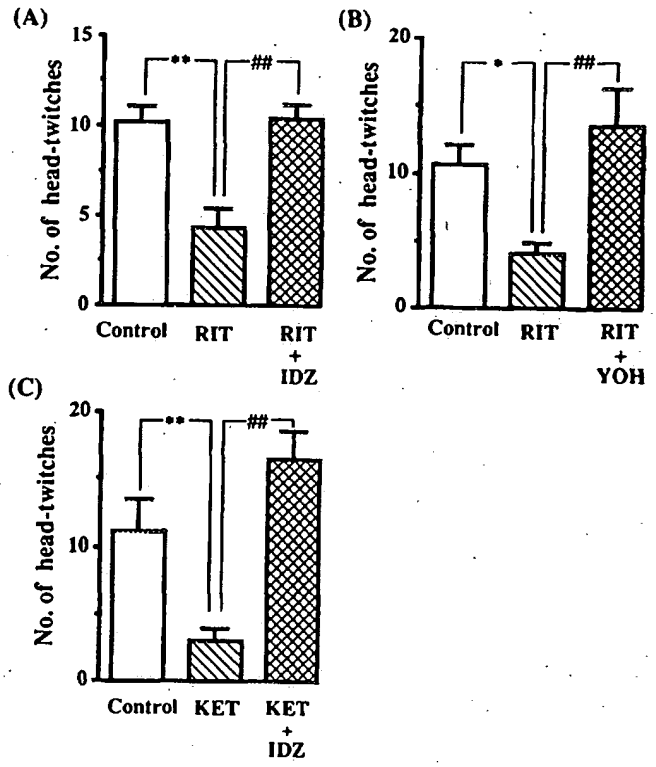

FIG. 2. Effect of idazoxan and yohimbine on the inhibition of the head-twitch response by selective 5-HT$_2$ receptor antagonists in normal mice. Idazoxan (0.2 mg/kg; IDZ; A and C), yohimbine (0.5 mg/kg, YOH, B) or saline was injected IP 30 min before 5-MeO-DMT (16 mg/kg). Ritanserin (0.03 mg/kg, RIT; A and B) and ketanserin (0.01 mg/kg; KET; C), or vehicle was injected s.c. immediately after administration of α2-adrenoceptor antagonists. Each datum represents the mean ± SEM (n = 10). *$p < 0.05$, **$p < 0.01$ vs. control. ##$p < 0.01$ vs. KET or RIT alone.

suppressed the head-twitch response caused by 5-MeO-DMT. Idazoxan at 0.5 mg/kg significantly reversed the prazosin (1.25 mg/kg) inhibition of the head-twitch response.

DISCUSSION

The 5-HT agonist-induced head-twitch response is known to be primarily mediated by postsynaptic 5-HT$_2$ receptor stimulation. In addition, drugs capable of interacting with adrenoceptors in the brain reportedly modulate this 5-HT$_2$ receptor-mediated behavioral response [14]. In the present study, clonidine, a selective α2-adrenoceptor agonist, decreased head twitches caused by 5-MeO-DMT, a 5-HT receptor agonist, and the effect was antagonized by the selective α2-adrenoceptor antagonists idazoxan and yohimbine, supporting the hypothesis that stimulation of α2-adrenoceptors negatively regulates the head-twitch response [13,16]. Moreover, in this study, we found that these α2-adrenoceptor antagonists, at doses that had no effect on the basal response, significantly reversed the inhibition of the head-twitch response by the selective 5-HT$_2$ receptor antagonists ritanserin and ketanserin.

Several factors may serve to explain the reversing action of α2-adrenoceptor antagonists. First, stimulation of α2-adrenoceptors by endogenous noradrenaline may be involved in this apparent antagonistic interaction between the effects of α2-adrenoceptor antagonists and 5-HT$_2$ receptor antagonists on the head-twitch response. This idea can be strongly supported by the finding that lesion of central noradrenergic systems with 6-OHDA plus nomifensine abolished the reversing action of idazoxan. Secondly, it is possible that facilitatory influence of endogenous noradrenaline on the head-twitch response through non-α2-adrenoceptors was unmasked by blockade of α2-adrenoceptors. In contrast to α2-adrenoceptors, the previous findings implicated β- and α1-adrenoceptors in facilitation of head-twitch responses caused by 5-HT receptor agonists [10,14]. Moreover, in this study, the selective α1-adrenoceptor antagonist prazosin exhibited a dose-dependent suppressive action on the 5-MeO-DMT-induced head-twitch response, and the effect was significantly reversed by idazoxan. Thus, noradrenaline inhibition of head-twitch response via α2-adrenoceptor may be counterbalanced by noradrenaline enhancement of the response via non-α2-adrenoceptors (such as α1-adrenoceptor).

However, it is unclear whether 5-HT$_2$ receptor-mediated head-twitch response is tonically regulated by endogenous noradrenaline through such mechanisms, since: 1) noradrena-

TABLE 1

CHANGES IN MONOAMIDE LEVELS IN THE BRAIN FOLLOWING TREATMENT WITH 6-OHDA PLUS NOMIFENSINE OR *p*-CPA

Regions/ monoamide	Treatment			
	Vehicle	6-OHDA + nomifensine	Vehicle	*p*-CPA
Cortex				
noradrenaline	0.349 ± 0.079	0.030 ± 0.006**	0.336 ± 0.035	0.254 ± 0.026
dopamine	0.144 ± 0.037	0.098 ± 0.027	0.142 ± 0.048	0.161 ± 0.083
5-HT	0.611 ± 0.051	0.566 ± 0.029	0.812 ± 0.125	0.313 ± 0.087*
Brainstem				
noradrenaline	0.825 ± 0.051	0.595 ± 0.049*	0.677 ± 0.030	0.636 ± 0.053
dopamine	0.117 ± 0.012	0.178 ± 0.015*	0.078 ± 0.023	0.052 ± 0.012
5-HT	0.962 ± 0.059	0.950 ± 0.058	1.039 ± 0.071	0.318 ± 0.036*

The animals were pretreated with nomifensine (5 mg/kg, ip). After 30 min, 6-OHDA (50 μg/mouse) or the corresponding vehicle was injected intracerebroventricularly. Seven days later, monoamine contents in the cortex and brainstem were determined. Each data represents mean ± SEM (μg/g tissue) of 5 mice. The numbers in the parentheses are % change. * $P < 0.05$ and ** $P < 0.01$ compared with respective vehicle control.

line depletion failed to change the basal number of head-twitches caused by 5-MeO-DMT and 2) the effective doses of idazoxan and yohimbine needed to attenuate the action of 5-HT_2 receptor antagonists were lower than those needed to increase the basal number of head-twitches in animals that received no 5-HT_2 receptor antagonist. This failure of noradrenaline depletion to alter basal head-twitches agrees with the data reported by Bednarczyk and Vetulani [2] and Orikasa and Sloley [21], although there is one report with conflicting results [14].

Done and Sharp [4] have demonstrated using a microdialysis technique that 5-HT_2 receptor antagonists enhance noradrenaline release in the rat hippocampus, and that 5-HT_2 receptors located on noradrenergic terminals play an inhibitory role in the release of noradrenaline. In this study, neither idazoxan nor yohimbine altered the basal number of head twitches at doses known to reverse the action of 5-HT_2 receptor antagonists. Taken together, it is possible to postulate that systemic administration of 5-HT_2 receptor antagonists enhances the function of noradrenergic systems involved in the regulation of head-twitch behavior, and that by blocking this enhancement of noradrenergic function, selective α2-adrenoceptor antagonists apparently antagonize the actions of selective 5-HT_2 receptor antagonists on head-twitch behavior. However, this possibility seem to be slight, if any, since the suppressive action of ritanserin did not significantly change following depletion of endogenous noradrenaline in the brain.

Endogenous 5-HT is reportedly involved in the 5-HT_{1A} receptor agonist-induced inhibition of the head-twitch response [5]. An increase in 5-HT release from 5-HT nerve

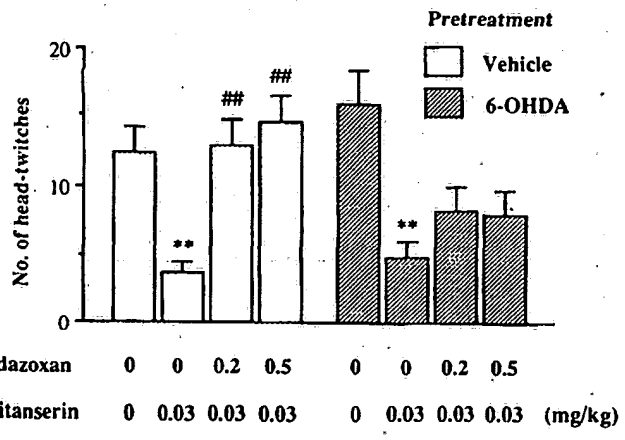

FIG. 3. Effect of 6-OHDA treatment on the apparent antagonistic action of idazoxan on ritanserin-induced inhibition of the head-twitch response. Mice were pretreated with 5 mg/kg (IP) nomifensine. Thirty minutes after nomifensine, either vehicle or 6-OHDA (50 mg/mouse, i.c.v.) was injected. After 7 days, the animals were used for the experiments. Ritanserin (0.03 mg/kg, s.c.) or idazoxan (0.2-0.5 μg/kg, IP) was injected 30 min before 5-MeO-DMT (16 mg/kg). Each datum represents the mean ± SEM ($n = 10$). ** $p < 0.01$ vs. respective control. ## $p < 0.01$ vs. ritanserin alone.

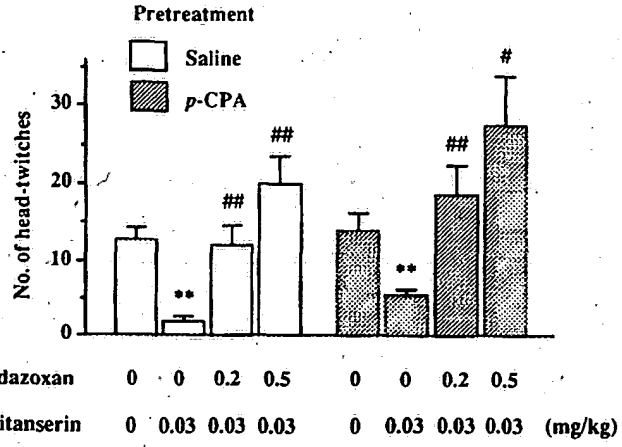

FIG. 4. Effect of *p*-CPA treatment on the apparent antagonistic action of idazoxan on ritanserin-induced inhibition of head-twitch response. Mice were treated with 3 doses of *p*-CPA (300 mg/kg, IP) 24, 48, and 72 hr before the experiments. Thirty minutes after the last treatment, the animals were injected with 5-MeO-DMT (16 mg/kg, IP). Ritanserin (0.03 mg/kg, s.c.) or idazoxan (0.2-0.5 mg/kg, IP) was injected 30 min before 5-MeO-DMT. Each datum represents the mean ± SEM ($n = 10$). ** $p < 0.01$ vs. respective vehicle control. # $p < 0.05$, ## $p < 0.01$ vs. ritanserin alone.

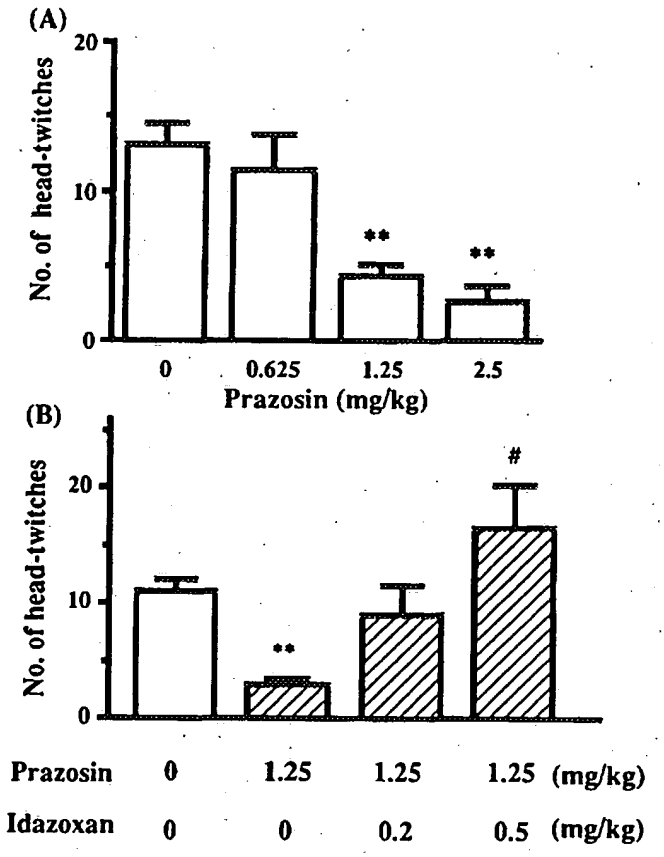

FIG. 5. Inhibition of 5-MeO-DMT-induced head-twitch response by prazosin, an α1-adrenoceptor antagonist, and idazoxan reversal of the inhibitory effect of prazosin. (A) Either prazosin or vehicle was injected IP 45 min before 5-MeO-DMT (16 mg/kg, IP) injection. (B) Prazosin (1.25 mg/kg, IP) and idazoxan (0.2-0.5 mg/kg, IP) were injected 45 and 30 min before 5-MeO-DMT (16 mg/kg, IP) injection, respectively. Each datum represents the mean ± SEM ($n = 9$). $^{**}p <$ 0.01 vs. vehicle control. #$p < 0.05$ vs. prazosin alone.

terminals also appears to be partly involved in the head-twitch response caused by quipazine, a direct 5-HT receptor agonist [18]. Furthermore, neurochemical evidence indicates that stimulation of α2-adrenoceptors located on serotonergic nerve terminals inhibits the release of 5-HT [6,9,19]. Together, blockade of α2-adrenoceptors which negatively regulate 5-HT release may be able to reverse the inhibitory effect of 5-HT_2 receptor antagonists. However, this does not seem to be the case since, in this study, pretreatment of animals with *p*-CPA did not attenuate the reversing effect of idazoxan on the head-twitch behavior suppressed by ritanserin. To clarify the exact mechanisms by which selective α2-adrenoceptor antagonists reverse the inhibition of head-twitch response by selective 5-HT_2 receptor antagonists requires further investigation. Nevertheless, the present findings indicate that endogenous noradrenaline stimulation of α2-adrenoceptors plays a role in the apparent reversing effect of selective α2-adrenoceptor antagonists.

The α2-adrenoceptors involved in the regulation of the 5-HT_2 receptor-mediated head-twitch response have been suggested to be on postsynaptic site of central noradrenergic nerve terminals. In addition, it has been hypothesized that such an α2-adrenoceptor is located "down-stream" of the 5-HT_2 receptor [10,16]. However, taking into account the data that the selective α2-adrenoceptor antagonists idazoxan and yohimbine reversed the effect of the selective 5-HT_2 receptor antagonists ritanserin and ketanserin implies that noradrenaline may decrease the ability of 5-HT_2 receptor agonists to stimulate 5-HT_2 receptors via stimulation of postsynaptic α2-adrenoceptors, by causing a conformational change in 5-HT_2 receptor protein, and that idazoxan and yohibine may attenuate the effect of ritanserin and ketanserin by reversing the decrease in the ability of 5-MeO-DMT to stimulate 5-HT_2 receptors.

5-HT_2 receptor agonists reportedly possess hallucinogenic activity in humans, and this activity is correlated with their affinities for the 5-HT_2 receptor subtype [7,8]. Moreover, there appears to be a similar correlation between the affinity of drugs for the 5-HT_2 receptor and their ability to inhibit head-twitch behavior in rodents [17]. Taken together, the present results suggest that the close linkage of adrenoceptors to 5-HT_2 receptors may also act to control the occurrence of hallucination triggered by 5-HT_2 receptor stimulation in humans.

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